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Short communication

Discovery of molluscicidal and cercaricidal activities of 3-substituted quinazolinone derivatives by a scaffold hopping approach using a pseudo-ring based on the intramolecular hydrogen bond formation

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ABSTRACT

Discovery of novel topological agents against *Oncomelania hupensis* snails and cercariae remains a significant challenge in current Schistosomiasis control. A pseudo-ring formed from salicylanilide by an intramolecular hydrogen bond led to the discovery of 3-substituted quinazolinone derivatives which showed a potent molluscicidal and cercaricidal activities.

1. Introduction

Schistosomiasis is the second most prevalent endemic disease after malaria in tropical and subtropical regions [1]. It is considered that at least 200 million people, in over 70 countries, are currently infected, 600 million people are at risk of infection, and about 200 000 deaths per year are associated with the severe symptoms [2]. Recent monitoring data revealed that schistosomiasis (*Schistosoma japonicum*) was re-emerging in China, especially along the Yangtze River and in the lakes region of Jiangxi and Hunan provinces [3]. Schistosomiasis control has attracted much attention again because of the continuous increase of infection cases though the disease was previously under control in China [4].

The lifecycle of schistosome includes adult worm, worm egg, miracidium larva, mother sporocyst, daughter sporocyst, cercariae, and schistosomulum steps [5]. The effective control of the disease should be based on an integrated approach incorporating chemotherapy, control of the snail host using molluscicides, and ecological and biological control methods to destroy the life cycle of schistosomes [6]. Nevertheless, eliminating snail played an extremely important role because of the expanding snail area, especially the spreading from epidemic region to historically snail-free area [7]. Meanwhile, the cercariae infecting their final hosts (e.g. man and mammals) by penetrating the skin are the key step resulting in schistosomiasis [8]. The cercariae are also the most frangible stage in their life cycle of schistosome. Killing the cercariae is the other efficient strategy to control the development of the disease [9,10].

Niclosamide, 5-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide (I), is the current salicylanilide molluscicide of choice in China and exhibits cercaricidal activities to cercariae of *S. japonicum* [11,12]. However, niclosamide suffers from some drawbacks involving lower solubility, expensive cost and hazard toxicity for aquatic plants, birds, fish and mammals. Also, it has to be applied continuously over a longer period of time to realize long-term snail control that may lead to drug resistance. Hence, developing of alternative new chemical molluscicidal and cercaricidal agents is

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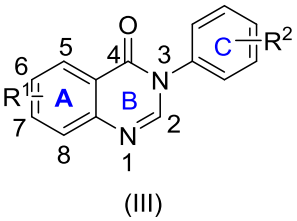
still highly desirable [13]. Niclosamide contains a fundamental structure of salicylamide, and the character of 2'-substituted Cl group makes it form a psedu six-membered ring via a strong hydrogen bond between OH and NH, taking a fairly rigid and planar conformation (II). The conformational similarity of (II) to 3-substituted quinazolinone (III) is based on the hypothesis that the pseudo six-member ring may function as a mimic of the pyrimidin-4(3*H*)-one ring of the 3-phenylquinazolin-4(3*H*)-one (Fig. 1) [14,15]. Recently, quinazolinone derivatives have been identified with novel anticancer, antitumor and antituberculosis inhibitors [16–18]. However, the molluscicidal and cercaricidal activities of quinazolinones have not been reported previously. Herein, we describe the synthesis and investigation of the molluscicidal and cercaricidal activities of 3-substituted quinazolinones derived from salicylanilide as potential drug candidates against schistosomiasis at transmission stages (see Fig. 2).



(III)

Fig. 2. The structure of 3-substituted quinazolinone.

2. Results and discussion

2.1. Synthesis

The synthetic route, chemical structure and yields of the products (**3a**–**3t**) were given in Scheme 1. Briefly, the 3-substituted quinazolinone were synthesized smoothly through $Bi(NO_3)_2$ catalyzed procedure by using 2-aminobenzoic acid, aniline and $CH(OEt)_3$ as the starting materials. The transformation was performed on the solvent-free conditions. To our delight, aryl-substituted amines proceeded smoothly to generate *N*-aryl substituted quinazolinones in good yields (**3a**–**3j**). The di- and tri-substituted anilines only affords the corresponding products in moderate yields owing to the steric effects (**3k**–**3r**). Furthermore, alkyl amines were also investigated and provided the desired product in moderate yields (**3s**–**3t**). The detail experiment process and characterization data were available in Supporting information.

2.2. Molluscicidal and cercaricidal activities

Oncomelania hupensis is the unique host in the transmission of *S. japonicum* in China, and also a target for molluscicidal studies. Meanwhile, control of cercariae of *S. japonicum* is an important approach to prevent the infection of man and mammals. The examination results of the synthesized compounds against *O. hupensis* snails and cercariae show their molluscicidal and cercaricidal potency (Table 1). Delightfully, all of the *N*-aryl substituted quinazolinones exhibited good activities (LC_{50} 2.69–10 ppm for snails and LC_{50} 0.68–2.51 ppm for cercariae, respectively). A loss of activity is observed with *N*-alkyl substituted (**3s** and **3t**). For example, **3s** estimated $LC_{50} > 100$ ppm, and hence it is considered inactive. It is worth noting that **3p** displayed the excellent molluscicidal and cercaricidal activities (the LC_{50} are 2.69 and 0.68 ppm, respectively). Although the comparison of the activities of the synthesized compounds with WPN showed our compounds were a little weak, **3p** still seems promising after some modifications which will be considered in a future study. The preliminary structure-activity relationship in the group of compounds **3a**–**3r** could be drawn from the experimental results: (1) The Cl group at the 6 position of the A ring was general more potent than NO_2. However, 6,8-dichloro-quinazolines produced inferior activities; (2) The aromatic rings were essential for C section; (3) The electron-donating groups on the C ring were optimal for activity.

2.3. Toxicity against tadpole

In order to explore the toxicity of **3p** to aquatic organisms for the future practical application in infected area, tadpoles were tested as models at 12, 24, 48 72, 96 and 120 h (Table 2). Control group lethality exhibited zero percent for the all experiments. For **3p**, the lethality of tadpoles did not occurred at the concentrations of 10 ppm–0.3125 ppm within the first 24 h. Only 10% average lethality occurred after 96 h at 5 ppm, so **3p** was of safety for aquatic organisms such as tadpoles within the effective cercaricidal concentrations from 0.3125 ppm to 2.5 ppm.

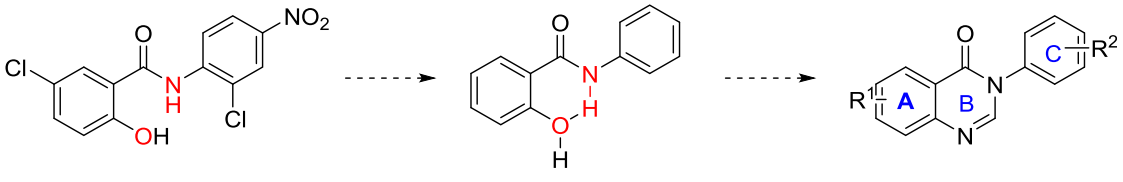
3. Conclusion

In conclusion, the pseudo six-membered ring formed by the intramolecular hydrogen bond in salicylanilides, which further lead to the discovery of 3-substituted quinazolinones through scaffold hopping approaches. The best compound **3p** displayed excellent molluscicidal and cercaricidal activities, as well as low toxicity. The electron-denoting groups on *N*-substituted aromatic ring are beneficial for the increase in the activity. The novel design strategy may offer a novel effective and environment-friendly approach to reduce the population infection rate. Further exploration of the SAR and molluscicidal and cercaricidal activities of the 3-substituted quinazolinones will be reported in due course.

4. Experimental sections

4.1. General

Melting points were measured using a melting point instrument and are uncorrected. The infra-red spectra were recorded on a Perkin–Elmer 1730 FT–IR spectrometer using KBr discs as stated.



(I) (II) (III)

Fig. 1. Scaffold hopping of niclosamide to 3-substituted quinazolinone.